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"Glial inhibition" of memory in Alzheimer's disease

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Two recent studies on *Nature Medicine* and *Nature Communications* reported the unusual roles of astrocytes in the brain, that is, release gamma-aminobutyric acid (GABA) and impair hippocampal memory in Alzheimer's disease (AD).

AD represents one common form of neurodegenerative diseases, and is characterized by progressive dementia. The pathological feature of an AD brain includes the appearance of amyloid plaques, fibrillary tangles and the associated loss of neurons. Neurophysiological and neurochemical examinations reveal the failures of synaptic transmission (especially the cholinergic modulation), altered expression of transmitter receptors and changes in the excitatory/inhibitory balance of transmission.

GABAergic transmission is the major type of inhibitory transmission in the brain, and accounts for 1/3 of all synaptic transmission. GABA is synthesized in neurons that express glutamic acid decarboxylase (GAD). The presynaptic spikes lead to the release of terminal vesicles and therefore the GABA onto the post-synaptic $GABA_A$ or $GABA_B$ receptors, contributing to the fast inotropic transmission through chloride channel, or slower metabotropic transmission through G-protein coupled potassium channel, respectively. The GABA in the synaptic cleft is then transported to the presynaptic terminal for re-utilization, or glial cells for further metabolism. Due to the lack of GAD in glia, the GABA is converted into succinic semialdehyde or glutamine in astrocyte, for instance.

GABAergic transmission is found to be altered at different stages of AD, in both animal models and human patient studies. The first line of evidence originated from radioligands of $GABA_A$ receptor agonists (such as benzodiazepine). The results suggested for well-preserved or mild loss of $GABA_A$ receptor binding site in hippocampus and cortical areas; while there is also evidence showing that the increased binding site in temporal cortex is due to the gliosis and the expression of GABA receptors on the glial cells. The second line of the proof was the analyses of GABA receptor protein and mRNA on animal models of AD or postmortem brain samples from AD patients. For instance, the $GABA_A$ α1 subunit which is important for benzodiazepine binding, was found to be reduced in hippocampus of AD brains; the levels for $GABA_A$ β2/3 subunits were found to be either preserved or slight decrease in different studies. Moreover, the AD pathological in postmortem hippocampus was correlated to the decreases in $GABA_B$ receptor R1 expression. GABA metabolism revealed by GAD function was also found to be impaired in different brain regions, including the cerebellum. The third line was the biochemical analyses of GABA concentration in the cortex and body fluids. The amount of GABA was found to be significantly decreased in temporal cortex and hippocampus from brains of AD patients, yet not well correlated to the neuropathological finding of plaques and tangles. The cerebrospinal fluid and plasma concentration of GABA are found to be reduced in AD patients as well. Recent advances of neuroimaging (such as magnetic resonance spectroscopy, MRS) further revealed the decreased GABA concentration at cer-

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tain brain regions in AD patients, such as parietal region.

The presence of GABAergic transmission and the loss of GABAergic neurons therefore lead to the paradoxical question that how GABAergic transmission changes in AD progression. This was recently answered by the fact that reactive astrocytes express GAD and release GABA through bestrophin 1 (best1) channel. Astrocytes were found to express GAD in development, physiological and pathological conditions, as well as in human tissues. Indeed, tissue fractionation analyses revealed that stronger GAD activities in brain tissues of mice model of AD was localized to glial synaptosomes from reactive astrocytes, compared to those of the wild-type mice. The mechanism of GABA release from astrocytes is found to be multiple, including the common intracellular calcium increase-mediated release, and through the best1 channel. Notably, astrocyte exhibits slow gliotransmission and lacks fast excitation; therefore, the GABA is continuously released once produced, contributing to the tonic inhibition on surrounding neurons in both hippocampus and cerebellum. In the two recent studies, Jo et al. [1] and Wu et al. [2] reported that GABA released from reactive astrocytes contributes to the hippocampal dependent memory formation, indicating a novel therapeutic target to alleviate AD behavioral syndromes.

Jo et al. [1] identified the aberrant GABA release from reactive astrocytes in APP/PS1 mice model of AD, and that the GABA is released through best1 channel, which is in line with their previous results on GABA release from astrocytes through this channel. Interestingly, they found that reactive astrocytes in hippocampus express minimal level of GAD, and that GABA is instead synthesized by monoamine oxidase-B (MAO-B) through putrescine degradation [1]. With MAO-B inhibitors, the authors successfully removed the tonic GABA inhibition on dentate gyrus (DG) granule neurons, revealed by the restoration of presynaptic stimulation-induced spike probability in these cells. Notably, the MAO-B inhibitor administration led to rescue of the impaired DG long-term potentiation (LTP), as well as the learning and memory ability in passive avoidance paradigm and Morris water maze in this mouse model of AD [1].

Wu et al. [2] reported similar results with a different mice model of AD, the 5XFAD mice. They showed the increased GABA content in hippocampus of post-mortem AD patient brains, in addition to the mice results [2]. However, instead of best1 channel, they reported upregulation of GAT3/4 on astrocytes as the upstream mechanism of enhanced GABA release, and increased expression of α5-$GABA_A$ receptors on DG granule cells as the increased downstream sensitivity to tonic inhibition, both of which contributed to the impaired DG LTP. The pharmacological applications of GAT3/4 inhibitor SNAP-5114 or α5-GABAA receptor inverse agonist L-655708 were found to ameliorate the working memory deficits in AD mice [2]. Notably, DG area has more A-beta plaque deposits compared to other hippocampal regions, such as CA1. Such circuit-specific disruption of synaptic transmission during neurodegeneration is yet to be studied in the future.

These studies provided the first link between astrocyte GABA release and the memory deficits in AD. Notably, both studies proved the therapeutic potential to alleviate the impaired memory with pharmacological compounds targeting the glial GABA production/release machinery. It will be interesting to examine if the GABAergic astrocytes observed in DG contributes to alteration of brain functions in other brain regions, such as parietal lobe, endorhinal cortex and piriform cortex. It has been estimated that 80% of hippocampal astrocytes contain GABA; in addition, most human astrocytes in culture express GAD and GABA metabolizing enzymes. These data emphasized the importance of gliosis in reaction to neurodegeneration: in addition to their roles in neuroinflammation, reactive astrocytes participate in synaptic transmission directly by controlling the strength of tonic inhibition.

Prior to the mechanistic discovery, GABAergic agonist or GABA transmission enhancer were found to treat the secondary symptoms (behavioral disruption) of AD. Interestingly, the GABAergic imbalance in AD has been linked to the impaired adult neurogenesis in hippocampus, in Apolipoprotein E4 (apoE4) knock-in mice [3], as well as human amyloid precursor protein (hAPP) transgenic mice [4], respectively. The loss of GABAergic interneurons resulted in the reduced maturation of new-born neurons in the DG, in consistency with the important roles of GABA in adult neurogenesis. Since adult generated neurons in hippocampus become DG granule cells, it will be very interesting to know if the impaired DG LTP is one downstream effect of impaired adult neurogenesis. It has been shown that reduction of adult neurogenesis influences the DG LTP and long-term depression. The addition of GABAergic astrocytes provided a new player in the relationship between adult neurogenesis impairment and AD [5].

Collectively, Jo et al. [1] and Wu et al. [2] provided strong evidence linking GABA release from astrocytes to brain function changes in AD. Their results may serve as common mechanism under other neurodegenerative diseases, and pave the way for further therapeutic efforts in searching for the novel pharmacological target, that is, removing the "glial inhibition".

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